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Mucormycosis attributed mortality: A seven-year review of surgical and medical management☆

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ABSTRACT

Introduction: Historically, mucormycosis infections have been associated with high mortality. The purpose of this study was to determine the incidence, associated mortality, and management strategies of mucormycosis in a major burn center.

Methods: A retrospective review was performed via obtaining all patients with mucormycosis admitted from January 2003 to November 2009 at our adult burn center was performed obtaining demographic data relevant to fungal burn wound infection or colonization.

Results: The incidence of mucormycosis at our facility was 4.9 per 1000 admissions; specifically, 11 military casualties and one civilian were diagnosed with mucormycosis. The median percentage Total Body Surface Area (TBSA) burned, 11 patients, or open wound, one patient, was 60 (IQR, 54.1 80.0), and the incidence of documented inhalation injury was 66.7% (8 of 12). Ten patients had surgical amputations. A median of eight days (IQR, 3.5 74.5) elapsed from diagnosis of mucormycosis until death in the 11 patients who expired. The overall mortality was 92%; however, autopsy attributed mucormycosis mortality was 54.5% (6 of 11) with all six patients having invasive mucormycosis.

Conclusion: Aggressive surgical intervention should be undertaken for invasive mucormycosis; additionally, implementation of standardized protocols for patients with large soft tissue injuries may mitigate mucormycosis superimposition.

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1. Introduction

In previous decades, changes in infection control procedures and advancements in topical and systemic antimicrobial chemotherapy have led to a decrease in the incidence of invasive gram negative burn wound infections and subsequent sepsis. Although bacterial burn infections remain the predominant culprit, invasive fungal complications have emerged as a significant source of morbidity and mortality in the severely burned patients [1,2]. Categorically, fungal

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Abbreviations: ICU, intensive care unit; IQR, inter quartile range; TBSA, total body surface area; CPG, clinical practice guideline; FWI, fungal wound infection; USAISR, United States Army Institute of Surgical Research; IRB, Institutional Review Board; MOSF, multi organ system failure; FWC, fungal wound colonization; RPG, rocket propelled grenade; IED, improvised explosive device; MOI, mechanism of injury; BG, (1→3) β D glucan; GM, galactomannan.

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Table 1 – Classification of microbial status of wounds.

Stage I: Wound colonization
Ia: Superficial colonization
Ib: Microorganisms in non viable tissue
Ic: Microorganisms at the interface of viable tissue
Stage II: Invasive infection
IIa: Microinvasion of viable tissue
IIb: Deep or generalized invasion of viable tissue
IIIc: Microvascular invasion

pathology is divided into fungal wound colonization and infections. The former is a fungal presence without penetration into viable tissue, while the latter describes an invasion of fungi into viable tissue below the eschar of a specimen. Further delineation of histopathological differentiation is depicted in Table 1 [3,4]. In humans, mucormycosis is caused by multiple specific fungal genus classifications such as *Rhizopus*, *Mucor*, and *Absidia* [5]. These pathogens are ubiquitous in the environment, soil and decaying organic matter, but rarely cause infection in healthy patients. The destruction of the skin barrier by the burn or traumatic wound combined with a dampened immune system make burn patients more susceptible to these invasive fungal infections. Although it is less commonly found in the burn wound compared to other fungi such as *Candida* and *Aspergillus*, mucormycosis is more likely to be invasive and is traditionally associated with a high mortality [6].

Mucormycosis is diagnosed by histopathological examination and/or fungal cultures. Histologically, mucormycosis appears as wide, ribbon like, but rarely septated hyphae. After diagnosis, mucormycosis is primarily treated with surgical debridement to achieve two objectives. First, resection is used to obtain a negative histopathological margin, which occasionally requires amputation to achieve source control. Second, the surgical debridement must proceed until viable tissue is identified to both rid the patient of necrotic tissue and improve bioavailability of systemic anti fungal therapy for mucormycosis with anti fungal agents such as amphotericin B.

Despite these treatments, development of mucormycosis in burn patients has been associated with a high mortality. Overall, fungal wound infection (FWI) has been found to be independently associated with mortality in burn patients with an odds ratio of 8.16 [7]. The overall mortality associated with fungal burn wound infection at our institution between 1991 and 2002 was approximately 76% [8]. The purpose of this study is to define the incidence and mortality of adult military and civilian patients admitted to our burn intensive care unit (BICU), and to describe the medical and surgical management strategies used to treat burn patients diagnosed with mucormycosis.

2. Methods

After obtaining approval from the hospital affiliated Institution Review Board (IRB), we conducted a retrospective review of all patients admitted to our burn center from January 2003 to November 2009. Inclusion criteria for the study was the presence of a thermal burn or traumatic injury with histopathological or fungal culture documentation of *Mucor*. Specifically, mucormycosis in this study is defined as the presence of *Mucor* on histopathological tissue sample or on fungal culture. Mucormycosis infection is defined as histopathological evidence of *Mucor* invasion into viable tissue; mucormycosis colonization is defined as the histopathological absence of *Mucor* invasion into viable tissue. Data collected included age, gender, percentage TBSA, presence of mucormycosis infection and/or colonization by histopathology and location, mortality, cause of death through retrospective autopsy evaluation when available or medical death report, days until diagnosis of mucormycosis after burn, days until death after diagnosis and treatment of mucormycosis, antifungal agents used, and operative management utilized. The number of operative procedures identified included relevant operative debridements and bedside histopathological excisional biopsies for mucormycosis. Admission burn sizes were estimated directly as a percentage of the total body surface area (TBSA) in standard fashion with the use of Lund Browder charts. Inhalation injury was diagnosed by bronchoscopy. While in isolated rooms in the BICU as an infection control strategy, all patients were examined daily for signs of infection during wound care by appropriately trained clinical staff. Additionally, daily multi disciplinary rounds discussed necessary empiric and therapeutic antibiotic and anti fungal therapy dictated by the patient's clinical status. Subsequently, the attending physician dictated surgical debridement, systemic anti fungal therapy, topical wound anti fungal agent and appropriate pre operative and post operative prophylactic antibiotics.

2.1. Statistical analysis

Continuous variables, such as age, post burn day, etc., are reported as medians (with interquartile ranges [IQR] the 25th and 75th percentiles). Categorical variables, such as mucormycosis infection, percentage TBSA burn injury, mortality, etc., are reported as numbers and percentages.

3. Results

Twelve of the 2453 patients admitted during the study period (4.9 per 1000 admissions) had evidence of mucormycosis on histopathological examination of biopsy specimens or fungal wound cultures. Eleven patients were identified by histopathological evidence of *Mucor* invasion or colonization, and one patient was found by fungal wound culture. Furthermore, 91.7% (11/12) of the patients were injured within Iraq or Afghanistan; all 11 of these servicemen suffered blast injuries including 90.9% (10/11) from improvised explosive devices (IED) and 9.1% (1/11) from rocket propelled grenade injuries. Patients with mucormycosis had a median age of 23.5 (IQR, 21.5 27), and a median burn or open wound size of 60% (IQR, 54.1 80) of TBSA. The incidence of inhalation injury was 66.7% (8 of 12). Seven patients had positive fungal wound cultures. Specifically, *Mucor circinelloides* was identified on cultures in two patients, *Saksenaea vasoformis* in one patient, *Sakesenaea erythrospora* in one patient and *Pythium aphanidermatum* in one patient [9,10]. The anatomic location most frequently involved

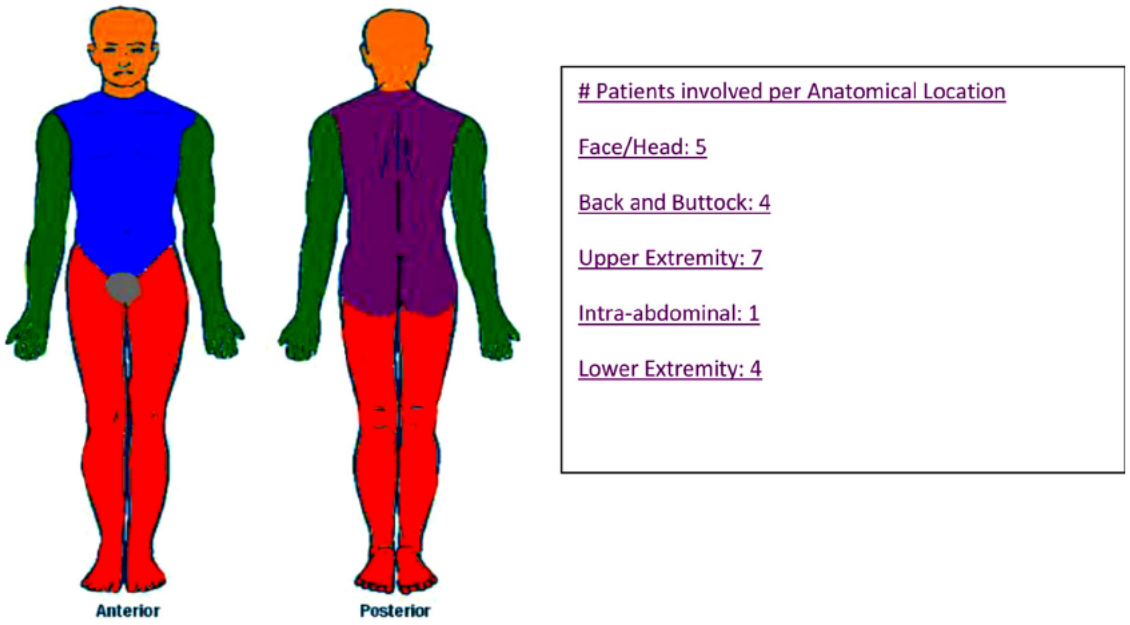

Fig. 1 – Anatomical distribution of mucormycosis.

by mucormycosis was an extremity (91.7%), as depicted in Fig. 1. Mucormycosis involved multiple distinct anatomical locations in 58.3% (7/12) patients with three patients having involvement of their head/face and upper extremity. Amputation occurred in 10 patients to achieve local control including one patient who underwent bilateral hip disarticulations. The median number of post burn or trauma days until diagnosis of mucormycosis was 14 (IQR, 12 16).

The overall mortality in these burned patients with mucormycosis was 92% (11/12), and in military patients it was 91% (10/11). The single surviving subject was found to have mucormycosis identified on histopathological examination of a

Table 2 – Mortality attributable demographics.

	Survived mucormycosis	Death attributable to mucormycosis	P value
# Patients	6	6	
Age	22.5 (20.5, 23.8) Max: 25 Min: 19	29 (23.5, 34.5) Max: 35 Min: 20	0.09
Mechanism of injury	4/6: IED; 1/6: RPG; 1/6 MVC	6/6: IED	0.45
TBSA	60 (39.5, 77.5) Max: 80 Min: 18	60 (56, 77.5) Max: 93 Min: 55.5	0.34
Inhalation injury	66.7% (4/6)	66.7% (4/6)	1.00
Histopathology	3/5: Invasion; 2/5: Colonization	6/6: Invasion	0.18
#Pre mucormycosis topical agents	2 (2, 2.8)	3 (2, 4)	0.14
# Pre mucormycosis systemic antibiotics	4.5 (3.3, 5.8)	4 (2, 4)	0.67
Pre mucormycoiss sulfamylon utilization	100% (6/6)	100% (6/6)	1.00
Operative procedures	2.5 (2.0, 3.0) Max: 4 Min: 2	2.5 (2.0, 5.3) Max: 7 Min: 2	0.50
Amputations	83.3% (5/6)	83.3% (5/6)	1.00
Mucormycosis present at Multiple Sites	50% (3/6)	66.7% (4/6)	0.56
Length of anti fungal treatment	15.5 (10.5, 28.0) Max: 82 Min: 0	6.5 (4.3, 16.3) Max: 81 Min: 2	0.42
Days from diagnosis to death	68 (8, 113) Max: 160 Min: 2	6 (3.3, 44.8) Max: 81 Min: 2	0.27
Days from completion of therapy to death	39 (0, 51) Max: 102 Min: 0	0 (0, 0) Max: 39 Min: 0	0.11

Table 3 – Specific treatment demographics of 12 patients with mucormycosis.

#	Surgical amputation	Anti fugal length of Tx	# OP	Outcome death note attributable mortality	Autopsy attributed mortality	A. Days from Dx to death	Days from completion of medical/surgical therapy to death
1	No	(A) 16 days	3	Death; No MSOF from GNR Sepsis 2. Burns 3. Coagulopathy Renal Failure	N/A	68	51
2	Yes Left (Hand)	(C) 8 days	2	Death; Yes 1. MSOF 2. TBI with Sagital Sinus Thrombosis 3. 55% TBSA 4. Renal failure 5. Hepatic failure 6. Pneumonia Fungemia	1. Craniocerebral Injuries 2.55.5% TBSA Integumentary Exam: Zygomycetes species fungus within necrotic muscle and demonstrates invasion	8	0
3	Yes (112 cm Small Bowel; Total Procto colectomy)	(A) 4 days	6	Death; Yes 1.64% TBSA 2. Invasive mucormycosis infection Sepsis	Infectious complications 1.(Klebsiella pneumonia sepsis and widely invasion Mucormycosis	4	0
4	Yes (Right Ear)	(A) 2 days	2	Death; Yes 1. Invasive Mucor Infection 2. 56% TBSA 3. Inhalational Injury 4. MDRO Acinetobacter Pneumonia 5. Renal Insufficiency	1. Invasive Fungal Infection (Mucor Meningitis) complicating 58% TBSA	2	0
5	Yes (Left Eye Enucleation); Multiple Digits on bilateral hands	(A) 81 days	7	Death; No 1.56% TBSA 2. MSOF 3. Sepsis & Bacteremia	No Final Diagnosis given; Invasive 90 degree branching fungal elements with invasion to viable tissue (IIa) from Face;	81	0
6	No	(V) 5 days (A) 14 days	3	Death; No 1. MSOF	Invasive abscess forming fungal infections complicating 73% TBSA burns Medium caliber, septate hyphae with dichotomous branching which invade into viable tissue	57	39
7	Yes (Upper Extremity digit (R))	(A) 8 days (V) 7 days	2	Death; Yes 1. Pan intestinal and Hepatic Infarct 2. Acute Renal failure Questionable Fungemia	N/A	8	0
8	Yes (Upper Extremity Digit)	None	2	Discharge home	N/A	NA	
9	Yes (Right Lower Extremity Above Knee Amputation)	(A) 2 days (F) 6 days (V) 1 day	2	Death; Yes 1. MSOF secondary to Aspergillus and Mucor 2. Burns	Complications from Thermal burn (77% TBSA) Fungal hyphae 45 degree colonized (No invasion)	2	0
10	Yes ((R) and (L) Ear	(A) 28 days (V) 4 days	3	Death; No 1.52% TBSA Burn 2. Sepsis 3. Pseudomonas bacteremia and pneumonia 4. Renal Failure 5. Pulmonary Failure	No final diagnosis entered; No Mucor identified to Integumentary exam	160	102

Table 3 (Continued)

#	Surgical amputation	Anti fugal length of Tx	# OP	Outcome death note attributable mortality	Autopsy attributed mortality	A. Days from Dx to death	Days from completion of medical/surgical therapy to death
11	Yes: Further Left Arm Amputation (6 cm) from prior amputation site	(V) 5 days	2	Death; No 1.82% TBSA 2. IED blast injury with traumatic amputation 3. Sepsis 4. Respiratory Failure 5. Rhabdomyolysis Acute Renal Failure	Complications of Burn and Blast Injuries: Multi organism bacteremia (*Acinetobacter baumannii* and *Pseudomonas aeruginosa*), lung abscesses, and infarct, and deep wound bacterial and fungal infections (Mucormycosis)	3	0
12	Yes (Bilateral Hip Disarticulations)	(A) 47 days (V) 6 days (P) 29 days	4	Death; No 1. MSOF 2. ARDS 3. Cardiovascular failure Sepsis/Bacteremia	Complications from Blast Injury 1. No evidence of inflammation or organism to Integumentary system	113	39

Abbreviations: V, Voriconazole; C, Caspofungin; A, Amphotericin B; OP, Operative Procedures; MOF, Multi System; Organ Failure; MDRO, Multi Drug Resistant Organism; TBI, Traumatic Brain Injury; ARDS, Acute Respiratory Distress Syndrome; GNR, Gram Negative Rods; IED, Improvised Explosive Device; TBSA, Total Body Surface Area.

digit amputated for severe burn necrosis with mucormycosis colonization (Ib) identified "after the fact", and was noted to have a fungal wound culture of *Mucor* species 27 days prior on his face. Therefore, the overall mortality from invasive mucormycosis in our series was essentially 100%. Specifically, autopsy attributed death to mucormycosis was present in six of the nine patients, as two of the patients who expired did not have a post mortem examined performed. The 12 patients are evaluated in Table 2 based on whether their death was attributed to mucormycosis, and their individualized specific mucormycosis surgical and medical treatments are listed in Table 3. Patient seven did not have an autopsy and his death note attributed his death to a "questionable fungemia". However, review of this chart revealed the subject's death was secondary to a pan hepatic and intestinal infarct, and likely not secondary to mucormycosis. Although mucormycosis angioinvasion can be responsible for thrombotic events, the absence of a definitive histopathological diagnosis precluded inclusion of this patient in the mucor attributed mortality. Five of these six patients were treated for mucormycosis surgically and medically with intravenous anti fungal agents until the time of their deaths. Although no statistical significance could be identified, all of these patients had an invasive fungal wound infection.

4. Discussion

The routine implementation of mafenide acetate (Sulfamylon®) and other topical anti microbials in burn care has facilitated the increase in opportunistic fungal wound infections in this immunocompromised patient population. Specifically, 100% of patients in this study were exposed to Sulfamylon prior to mucormycosis diagnosis by histopathological or tissue culture results. Additionally, the 12 patients were exposed to 4 (IQR, 3 5) different systemic antibiotics prior to histological or tissue culture diagnosis of mucormycosis. No identifiable differences were found in the utilization of topical agents and systemic antibiotics prior to development of mucormycosis between patients with mortality attributable to mucormycosis and those who survived mucormycosis. Topical and intravenous antibiotics are used liberally in severely burned patients, and their application likely contributes to the development of fungal infections in this population.

A retrospective review, done at our facility between the years of 1954 1983, identified 105 patients with a tissue diagnosis of phycomycosis. During this study period, the highest incidence was in 1969, which correlates temporally with the Vietnam War [11]. Our incidence of mucormycosis from 2003 to 2009 was 4.9 per 1000 admitted patients. This is comparable to a prior study at our facility performed with 2114 patients (1979 1989), who had an incidence of infection (with *Mucor* species and *Rhizopus* species) of 6.1 per 1000 admissions. Importantly, FWI has been associated with 14% attributable mortality, with an odds ratio of death of 8.16. This effect is equivalent to increasing the TBSA by 33%.

Mucormycosis is a rare fungal infection that demonstrates minimal intrinsic pathogenicity in healthy people; however, burn wounds are unique in that they severely impair the immune system thus increasing a patient's susceptibility to *Mucor* infections and fulminant superinfections [12]. In addition to appropriate systemic anti fungal therapy, treatment for mucormycosis includes wide operative debridement to healthy, vascularized tissue. This removes necrotic tissue which acts as a nidus for fungal proliferation [13]. From our experience, these infections do not respect anatomic limits or

barriers, and may necessitate amputations for infection control. Despite aggressive debridement, survival cannot be expected in most victims. Ten of the 12 (83.3%) patients in this study underwent amputation with only one patient surviving to discharge. Seven patients were still being treated for mucormycosis at the time of their death.

Autopsy and death note analysis demonstrated an attrib utable mortality of mucormycosis of 58.3%. Early diagnosis prior to viable tissue invasion is the single most important aspect of mucormycosis management. Current research into fungal serological assays, such as (1→3) β D glucan (BG) and galactomannan (GM) assays, has not demonstrated a clear association with fungal wound infection, fungal wound colonization, or species of fungus isolated from patients with a fungal wound colonization or infection [14]. To the detriment of the patient, mucormycosis is insidious and diagnosis is often delayed. Such factors prompt the consideration for active wound surveillance. Specifically, fungal wound cultures diagnosed *Mucor* species in 7 out of 12 patients. Prior reports from our institution have demonstrated mucor like morphol ogy was only able to be captured 40% of the time on fungal wound culture. Identification of these fungal infections in a timely fashion requires a high index of suspicion and may encourage implementation of an institute specific surveil lance program for fungal wound colonization/infection. This has been suggested in Keen's et al. article for evaluation of bacterial multi drug resistant species of *Acinetobacter* and *Pseudomonas*; specifically, the utilization of a bedside culture and/or histological biopsy from wounds would serve as an adjunctive measure in addition to more traditional means of clinical evaluation [15].

For healthcare professionals practicing in war zones, the patient population most at risk for FWI are those suffering blast injuries, especially casualties with extensive lower extremity and/or perineal soft tissue loss and traumatic amputations. In our study, the median time from injury to diagnosis for these FWI was 10 days [16]. A wound surveillance screening clinical practice guideline for fungal infections is currently deployed within the military health care system. The Joint Theater Trauma System Clinical Practice Guidelines, *Treatment of Suspected Invasive Fungal Infections in War Wounds*, was created to standardize the care of these injuries, from wounding to hospitalization, in order to systematically minimize the mortality from these predisposed wounds for active fungal wound infections [17].

Recently, a tornado in Joplin, Missouri was associated with 13 cases of mucormycosis infections, secondary to the rare species, *Apophysomyces trapeziformis* [18]. The mortality of the victims was reported to be 38% (5 of 13 cases) with all 13 patients undergoing an average of four surgical debridements. The article does not include the histopathological level of colonization or invasion or whether formal amputations occurred. Consequently, the unifying theme of mucor infec tions is that of a large, open wound often with residual necrotic tissue regardless of the mechanism of injury that creates it, be it a tornado or an improvised explosive device. As such, mucormycosis is an ominous indication of an over whelming wound burden that mandates immediate and aggressive surgical intervention and systemic anti fungal therapy to circumvent further destructive fungal invasion. As illustrated by our experience in Afghanistan and Iraq, this often requires amputation to eradicate the fungus and lessen the wound burden.

This study has several limitations. First, this is a retrospec tive study and has all the inherent risks of this study design. Second, several of these patients suffered injuries prior to the CPG implementation, and may have benefited from earlier recognition and more aggressive initial surgical and/or in patient management strategies. Third, the 11 military patients underwent surgical interventions performed by providers from Afghanistan to Germany to the United States; this variability, especially given the small number of patients in our study, makes it difficult to derive any solid conclusions. Finally, the delay in histopathological diagnosis from wound culture or excisional tissue biopsy may have impeded initial implementation of medical and/or surgical therapy.

5. Conclusion

The incidence of mucormycosis at our burn center is 4.9 per 1000 admissions during this war period which is slightly lower than previously reported at USAISR. All six patients with mortality attributable to mucormycosis had invasion into live tissue (Stage II). We recommend that once recognized, all FWI undergo immediate surgical debridement so that only viable tissue remains and the wound is free of fungus on histopath ological examination. This requires tissue biopsy confirmation of 'clear margins,' which may take a day or more for laboratory processing. It is therefore incumbent on the surgeon to aggressively remove all suspicious tissue even if this means violating anatomic tissue planes to ''stay ahead of the fungus,'' and necessitates frequent returns to the operating room for confirmation of fugal eradication. It may also require early and high amputation(s) and/or disarticulation(s) of an injured extremity. The goal of operative debridement is to remove all necrotic and/or infected tissue; but ultimately, survival will depend on wound closure to protect the remaining tissue from FWI and to reduce the metabolic burden on the patient. Amputations and/or disarticulations, although seemingly heroic measures in these cases, may expeditiously affect both goals, especially reducing the wound burden to a manageable size. While concomitant systemic anti fungal therapy may improve outcomes, extensive surgical debride ment remains the first line therapy, since necrotic tissue, which is the nidus for FWI, is not perfused when antifungal agents are given intravenously. Burn and trauma centers must remain vigilant for the presence of invasive fungal infection in severely injured patients with soft tissue injuries as early detection and aggressive surgical therapy, combined with systemic antifungal therapy, may improve outcomes. Fur thermore, combat casualties suffering blast injuries, IED or RPG, are at an increased risk of acquiring highly lethal mucormycosis, and military personnel must remain vigilant when caring for these severely injured patients to closely monitor for the development of mucormycosis. Consideration of a standardized protocol and/or surveillance cultures with adjunctive empiric anti fungal therapy should be standard of care in those with extensive soft tissue injuries, especially in the setting of war, major civilian trauma or natural disasters.

IRB approval

This study was conducted under a protocol reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol.

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